Synthetic biology and patents

A European perspective

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The patent system has evolved over many centuries and is considered, by and large, to have successfully promoted innovation. Patents help to stimulate investment in research and development through the provision of a limited monopoly to the inventor, while ensuring full disclosure of the invention to the public. One of the reasons for the long-lasting success of the patent system is its non-discriminatory character. The same basic patentability criteria apply to all fields of technology: novelty, inventive step and industrial application. This provides legal certainty to the applicant and third parties because the criteria applied during examination at the patent office—and in courts—are largely independent of the nature of the invention. The World Trade Organization (WTO; Geneva, Switzerland) Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS), which was negotiated in 1994, includes a provision that underlines this technology-neutral character of patents: Article 27(1) states that “[...] patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application”.

Nevertheless, the emergence of new technologies regularly raises the question of whether the patent system, which was historically designed to protect mechanical inventions, and was only later extended to chemical products and processes, is suitable to protect inventions in fields as new as synthetic biology. Perhaps more importantly, it also raises the issue of whether the patent system is, or has been, able to promote the advancement of these new technologies. Similar questions were also raised some years ago, as the patenting of biotechnology

and computer-implemented inventions—that is, software—gathered momentum. The European Parliament (Strasbourg, France), after a 10-year debate, concluded Directive 98/44/EC on the legal protection of biotechnological inventions; this was later implemented in the regulations of the European Patent Convention (EPC), which is an intergovernmental treaty that establishes a common legal framework for patents in 36 European member states. The provisions in this directive specify further requirements for biotechnological inventions in order to be patentable and define subject matter that can not be patented—such as processes for the cloning of human beings or the industrial and commercial use of human embryonic stem cells. A similar attempt to adopt a directive for the protection of computer-implemented inventions failed in 2005 after vigorous debate in the European Parliament.

Some economists have commented that patents might hinder innovation in synthetic biology, rather than promote it (Rai & Boyle, 2007; Henkel & Maurer, 2007; Calvert, 2008; Bhutkar, 2005). Some environmental groups have gone so far as to request an outright ban on technologies arising from synthetic biology and any patents related to it (ETC Group, 2007). Is synthetic biology really so different from classical biotechnology that further provisions governing patentability are justified? This question can, of course, be asked from many perspectives, the most important ones being technological, legal, ethical, social and economical (Balmer & Martin, 2008).

A report for the European Commission (EC; Brussels, Belgium) provides the following definition: “Synthetic biology is the engineering of biology: the synthesis of

complex, biologically based (or inspired) systems which display functions that do not exist in nature. This engineering perspective may be applied at all levels of the hierarchy of biological structures—from individual molecules to whole cells, tissues and organisms. In essence, synthetic biology will enable the design of ‘biological systems’ in a rational and systematic way” (EC, 2005).

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In the scientific literature, one can distinguish at least three general approaches to synthetic biology. The first approach aims to modify existing organisms in order to achieve desired functionalities, such as the production of certain metabolites. This approach is similar to metabolic engineering, but applies the increasing knowledge of ‘genetic circuitry’ and aims to develop engineering-like standardized practices. The second approach starts by using simple, chemical building blocks, such as nucleotides, to synthesize genes or even whole genomes, which can then be transplanted into cells that have been purged of their own genetic material, thereby generating a ‘synthetic organism’. In an extension of this approach, synthetic ‘protocells’ are developed that mimic some properties of living cells. An older and simpler variation of this approach is the generation of infectious viruses by chemical synthesis (Cello *et al.*, 2002). Philosophically, the

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second approach is certainly revolutionary as it comes closer to the ancient dream or nightmare of life being generated from non-living material—stories relating to the creation of a golem by Judah Loew ben Bezalel (circa 1520–1609), and the homunculus as imagined in *Faust* by Johann Wolfgang von Goethe (1749–1832), are literary accounts of this idea. However, so far, the creation of ‘life from scratch’ has not been achieved, as complex biological systems are still required to harbour the synthesized genomes. The last approach aims to reduce the complexity of naturally existing organisms by deleting ‘superfluous’ genes, which are, to a large extent, required for adaptation to diverse environments. The resulting ‘minimal genome’ organisms are only viable in rich, artificial media, which contain many of the nutrients that a ‘natural’ organism would synthesize itself. The idea behind this strategy is the generation of ‘streamlined’ microorganisms that are perfectly adapted and highly efficient for a specific—that is, industrial—task.

In summary, it seems difficult to distinguish synthetic biology from long established fields of biotechnology such as metabolic engineering or recombinant protein expression. The difference seems to reside more in the scale of modification of naturally occurring organisms—involving tens to hundreds of genes in synthetic biology—and in the underlying concepts—an engineering approach (partregistry.org) or the creation of artificial life (Anon, 2007)—than in the actual technologies used. Moreover, many of the building blocks or ‘parts’ (Endy, 2005) used for synthetic biology are identical to those used in other areas of biotechnology.

From the point of view of European patent law, it seems difficult to envisage specific provisions for synthetic biology. Article 53(b) of the EPC ascribes “Exception to patentability of plant and animal varieties and essentially biological processes for the production of plants or animals”. This explicitly excludes microbiological processes and the products

thereof from the exception—that is to say, microorganisms are patentable. The specific provisions for biotechnological inventions as laid down in Rules 26–29 of the EPC explicitly allow the patentability of biological subject matter, such as proteins or nucleic acids, provided that their industrial application is described in the patent application. As patent applications in the field of synthetic biology are likely to contain claims for biological molecules or microorganisms, methods for their production, or uses of such molecules or microorganisms, they are mostly indistinguishable from applications in other areas of biotechnology. Patents on nucleic acids, proteins or microorganisms have been granted for many years and often confer protection irrespective of their possible use in different technologies (EPO, 2009). For this reason, it is also difficult to estimate the number of patents and patent applications relating to synthetic biology.

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Article 53(a) of the EPC excludes from patentability “inventions the commercial exploitation of which would be contrary to ‘ordre public’ or morality”. So, one might ask whether specific synthetic biology inventions could fall under this provision. An example could be the use of synthetic biology to produce biological weapons; such an endeavour would be similar to a ‘letter bomb’, which is regularly used to illustrate the exception under Article 53(a) of the EPC. For other, less drastic, applications of synthetic biology, the interpretation of Article 53(a) is more complex, and depends on the circumstances and the specific content of the patent application. The question, for example, of whether the creation of ‘artificial life’ in itself, or its patenting, could be considered immoral has, to my knowledge, not been explicitly addressed by any legal authority to date. However, case law under the EPC has confirmed the patentability of microorganisms and higher life forms—that

is, plants and animals—including genetically modified forms, which could also be considered ‘artificial’. In most cases it seems, therefore, unlikely that synthetic biology will be considered “contrary to ‘ordre public’ or morality” in the sense of the EPC.

From a social and economic point of view, there are questions about the effectiveness of patents in promoting innovation and in providing access to the results of such innovation. Here, the basic rationale of the patent system mentioned at the beginning of this article again comes into play. With regard to the promotion of innovation, some crucial characteristics of synthetic biology might be listed in comparison to ‘classical’ biotechnology.

The first of these is interdisciplinarity. Synthetic biology often combines approaches from various disciplines, such as biotechnology, chemistry, nanotechnology, computing and engineering. This requires patent offices and patent professionals to be proficient in all of the technical domains involved. It puts a high burden on recruitment and training to ensure that the relevant prior art is found and judged correctly. Moreover, synthetic biology involves two areas, biotechnology and computing, both of which are at the centre of the public debate about patents. Some observers have therefore predicted a ‘perfect storm’ with regard to patents in synthetic biology (Rai & Boyle, 2007).

The second is complexity. Synthetic biology often involves many ‘parts’—as some in the synthetic biology community have called the genetic entities used in synthetic biology—that work together to achieve a certain effect. In this respect, synthetic biology might be closer to technical areas such as telecommunication or computers, as well as to some research tools and diagnostic devices—such as microarrays—in which many components interact in a single product. A product generated by synthetic biology—for instance, a bacteria producing biofuel—can involve hundreds of different parts that, in the extreme, might all be protected by different patents that are probably held by several rights holders, thereby creating a so-called patent thicket. One early example is genetically modified ‘golden rice’—actually developed before the term synthetic biology was widely used—for which more than 70 patent rights needed to be cleared (Potrykus, 2001). This situation

can make negotiations difficult and costly. A way to circumvent patent thickets is to use cross-licenses between patent holders or to create patent pools or clearing houses.

Interconnectedness, interoperability and standardization are further characteristics of synthetic biology that could generate the potential for hold-up situations. If a single part has become a standard or has been used so often that it has acquired a quasi-standard character, the actors in the field become 'locked-in'—they completely depend on that part, which in turn creates big opportunities for the rights holder of that part. So-called patent trolls or patent sharks—companies whose only business model is to sue others and charge license or settlement fees without producing anything themselves (Henkel & Reitzig, 2008)—might profit here.

Security and safety are given particular attention in the public arena, as some argue that synthetic biology technology could be used to produce harmful micro-organisms or viruses. Patent applications are published 18 months after their first filing, and the biological sequences disclosed therein are made available free of charge in online databases. In theory, information about disease-causing or pest-causing biological agents disclosed in patent applications could be used for malicious purposes. From a practical point of view, it could be argued that nature already provides plenty of harmful micro-organisms that would make the generation of new artificial biological agents for use in terrorism seem unlikely. However, the development and intentions in this area are difficult to predict, and so the discussion about the disclosure of scientific papers and patents in this area is likely to continue (Frischknecht, 2003).

Given these characteristics of synthetic biology, it seems possible that specific socio-economic problems might arise with patents in this field. What could make these problems harder to tackle is the current state of the patent system: worldwide, there are increasing numbers of applications, new subject areas being covered by patents, and new players such as venture capitalists, IP fund managers and patent auction houses coming on the scene. Patent offices around the world are accumulating backlogs of unexamined patent applications, which generates legal uncertainty. Although this is less pronounced in Europe,

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and in biotechnology, it can still generate problems when attempting to analyse the legal status of a patent application.

At least three responses on the part of patent offices and regulators can be envisaged to counteract these trends: first, to maintain or even raise the bar of patentability, that is, to make sure that no patents are granted for obvious or even trivial subject matter; second, to make sure that patent rights have clear boundaries and are examined without much delay to provide legal certainty; and third, to ensure that patents and the patenting process are transparent, and easily detectable and retrievable by everybody working in the field. At the European Patent Office (EPO; Munich, Germany), the whole patenting process is made public through online file inspection—all communications between the applicant/patentee and the EPO are available (epoline.org; ep.espacenet.com).

However, finding a patent application on a specific topic can resemble the famous search for a needle in a haystack, particularly for scientists who are not familiar with patent searching and classification. It is even more difficult to analyse whether patents or patent applications exist that cover certain subject matter. This last aspect becomes especially important when one wants to determine 'freedom to operate' or to identify areas that are public domain—that is, when not covered by property rights. The success of projects such as the Massachusetts Institute of Technology Registry initiative (Cambridge, MA, USA), which follows an open-source philosophy, will probably depend on the ability to delineate clearly what is already protected and by whom.

To check, for example, whether a specific sequence—a 'part' or BioBrick™—deposited in the registry is already covered by a patent application or a patent, one would first have to launch a sequence search in all available patent sequence databases. The relevant hits would then have to be checked individually for the legal status

of the underlying patent applications or patents—pending, refused, granted or withdrawn, for example. The geographical coverage of the patent applications or patents is equally important, because patent law is territorial and protection exists only for the territory in which a patent has been granted; an EPO patent, for instance, does not provide protection in the USA. Furthermore, for pending or granted applications, it would be necessary to check which claims are currently being considered or are already granted, because the scope of claims can change substantially during patent proceedings. Finally, the actual or granted claims would have to be analysed to find out whether the part of interest is covered by the scope of the claims. Only after such an analysis could a (provisional) statement be made as to the coverage or non-coverage of the specific part by patents or patent applications.

Determining what is already covered by patent rights therefore remains a particular problem for small and medium-sized companies, and for academics. In a field such as synthetic biology, in which one engineered micro-organism might involve hundreds of different parts and processes, this problem becomes aggravated. There is some hope, however, that modern text-mining and computer-search technologies will help to make such an analysis of 'freedom to operate' easier and economically more feasible in the future.

Finally, it should be noted that patents are not responsible for everything and they also cannot solve everything. This applies to ethical and social, as well as economic, questions. One should not forget that there is 'life after grant', and that other regulatory means are available to deal with some of the problems indicated here, such as the regulation of ethically sensitive research, the research exemption for the use of patented subject matter, the control of anti-competitive behaviour and provisions for access to life-saving medicines. Furthermore, as governments or philanthropic organizations fund a lot of research in synthetic biology, they can exercise their influence on the licensing conditions for the resulting patents. It remains to be seen, however, how synthetic biology will develop, and what role patents can play to foster investment and advancement in this exciting new technology (Rutz, 2007).

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The present article is based on personal considerations by the author and does not necessarily reflect the official position of the EPO on the subject.

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doi:10.1038/embor.2009.131